



Published in final edited form as:

Curr Top Dev Biol. 2019 ; 135: 287–313. doi:10.1016/bs.ctdb.2019.04.002.

Sperm success and immunity

Stuart Wigby^{a,*}, Susan S. Suarez^b, Brian P. Lazzaro^b, Tommaso Pizzari^a, Mariana F. Wolfner^b

^aEdward Grey Institute, Department of Zoology, University of Oxford, Oxford, United Kingdom

^bDepartments of Biomedical Sciences (SSS), Entomology (BPL), and Molecular Biology and Genetics (MFW), Cornell University, Ithaca, NY, United States

Abstract

The moment of the fertilization of an egg by a spermatozoon—the point of “sperm success”—is a key milestone in the biology of sexually reproducing species and is a fundamental requirement for offspring production. Fertilization also represents the culmination of a suite of sexually selected processes in both sexes and is commonly used as a landmark to measure reproductive success. Sperm success is heavily dependent upon interactions with other key aspects of male and female biology, with the immune system among the most important. The immune system is vital to maintaining health in both sexes; however, immune reactions can also have antagonistic effects on sperm success. The effects of immunity on sperm success are diverse, and may include trade-offs in the male between investment in the production or protection of sperm, as well as more direct, hostile, immune responses to sperm within the female, and potentially the male, reproductive tract. Here, we review current understanding of where the biology of immunity and sperm meet, and identify the gaps in our knowledge.

1. Introduction

The production of sperm via spermatogenesis is well-understood from many perspectives (e.g., reviewed in Nishimura & L’Hernault, 2017). However, within the male, there is a potential trade-off between the energy demands required for making high-quality sperm and the demands of protecting the soma from infectious disease. Moreover, the female reproductive tract is a potentially hostile environment that contains molecules and cells that protect the female from infection but that may also be harmful to sperm. These defenses include a low pH and reactive oxygen species, an abundance of antimicrobial peptides, scavenging macrophages, and, in vertebrates, antibodies generated by the acquired immune system. Although they may be immunologically protective in intent, these chemical and cellular defenses have the potential to impair sperm viability or function (i.e., sperm success). Here, we discuss the interactions between sperm and the immune system, delineating areas in which function of one can impair function of the other (summarized in Fig. 1). The main themes we consider are (1) energetic trade-offs between investment by males in making sperm or by males and females in maintaining viable sperm versus

*Corresponding author: stuart.wigby@zoo.ox.ac.uk.

investment in the immune system; (2) shared genetics, such as where specific genes have pleiotropic sperm- and immune-related functions; (3) the impact of infections in males and females, both somatic and sexually transmitted, on sperm; (4) immune responses directly against the sperm in males and females; and (5) the role of immunity in sperm selection by female choice.

2. Sperm success and the male immune system

In the next sections, we describe how relationships and interactions between sperm and the male immune system can be both harmful (Sections 2.1–2.4) and helpful (Section 2.4) to sperm success (Fig. 1).

2.1 Expensive ejaculates and trade-offs with immunity

Given the relatively small size of sperm cells in most species (among the smallest cells in the body) in comparison to ova (among the largest), the production of sperm was once thought to be energetically cheap (Gee, 1999). However, biologists have since begun to realize that (1) males are typically limited in their ejaculate production rate; (2) females often mate with multiple males, which leads to sperm competition, in which rival ejaculates compete for access to eggs; and (3) sperm competition favours ejaculates with larger numbers of sperm (and potentially more seminal fluid) to increase their probability of winning fertilizations (Birkhead & Pizzari, 2002; Cameron, Day, & Rowe, 2007; Dewsbury, 1982; Parker, 1970; Perry, Sirot, & Wigby, 2013; Wigby & Chapman, 2004). These findings have led to the theory that males should strategically allocate sperm and seminal fluid across different matings in order to maximize their reproductive returns (Cameron et al., 2007; Parker, 1990; Parker et al., 1996). This newer perspective has now gained extensive empirical support from studies across a range of vertebrate and invertebrate species (Garbaczewska, Billeter, & Levine, 2013; Hopkins, Sepil, & Wigby, 2017; Kelly & Jennions, 2011; Sirot, Wolfner, & Wigby, 2011; Wigby et al., 2009). To increase their reproductive success, males (particularly in polyandrous or polygynandrous species) must devote considerable resources into developing large testes and accessory glands, and into using those organs to produce large volumes of sperm and seminal fluid. Together, these factors point toward non-trivial costs of ejaculate production which, in extreme cases, can lead to situations where females become sperm-limited because they fail to receive sufficient sperm from a single mating to fertilize all their eggs (Wedell, Gage, & Parker, 2002).

The fundamental assumption of life-history theory is that resources allocated to one trait will trade-off against those needed for other traits (Zera & Harshman, 2001). Ejaculates are no exception: the cost of producing them is expected to decrease resources available for other important life-history traits. The idea of such trade-offs has received empirical support from studies that suggest that investment in ejaculates compromises traits involved in attracting mates, such as ornaments or weapons (Parker & Pizzari, 2010; Simmons & Emlen, 2006; Simmons, Lüpold, & Fitzpatrick, 2017). Nevertheless, some of the most compelling evidence for trade-offs involving ejaculates comes from negative correlations between ejaculate quality and somatic immunity. The idea of an antagonistic relationship between male sexual and immunological physiology has been widely recognized in evolutionary

biology, since Folstad and Karter (1992) suggested the “immunocompetence handicap hypothesis.” In vertebrates, testosterone is vital for the development of male reproductive traits, but it also suppresses immunity. The immunocompetence handicap hypothesis posits that these antagonistic effects could make male sexual characteristics reliable indicators of general male genetic quality or condition—and thus targets for sexually selected female preferences—because high levels of sexual characteristics provide evidence that those males can cope with testosterone-mediated immune suppression. A similar logic can apply to primary male sexual characteristics, whereby high testosterone levels should be associated with large testes and high-quality ejaculates, yet result in reduced immune function. In support of these ideas, negative relationships have been found between the size of the testes and the size of the spleen—which has important immune functions—in bats, Cape ground squirrels *Xerus inauris*, and Arctic char *Salvelinus alpinus* (Hosken & O’Shea, 2001; Liljedal, Folstad, & Skarstein, 1999; Manjerovic & Waterman, 2012; Roberts, Buchanan, & Evans, 2004). These data are broadly consistent with a testosterone-mediated ejaculate-immunity trade-off (assuming that testes and spleen size are reliable indicators of general testosterone and immunity levels, respectively). Nevertheless, the data do not uniformly support the concept of costly ejaculates. While a positive relationship between testes size and lice burden was found in the Cape ground squirrel (Manjerovic & Waterman, 2012), nematode infection (also an indication of depressed immunity) was negatively associated with ejaculate quality in arctic char (Liljedal et al., 1999). The complete picture is therefore one in which the consequences of investment in ejaculates for realized resistance to parasites may vary according to the taxa of the host and/or parasite.

The potential for trade-offs in males between immunity and the ejaculate is not limited to vertebrates. Studies on insects, which lack testosterone, also provide evidence in support of the immunocompetence handicap hypothesis. For example, removal of sexual selection in dung fly *Scatophaga stercoraria* populations, via experimental evolution under enforced monogamy, results in the evolution of decreased testis size, but increased phenoloxidase activity (Hosken, 2001). Since phenoloxidase is an important component of the insect innate immune system, these results are consistent with a testes-immunity trade-off. In field crickets *Teleogryllus oceanicus*, negative genetic and phenotypic correlations between sperm viability and lysozyme activity (Simmons & Roberts, 2005), and a diet-dependent reduction in viability under immune challenge (Simmons, 2011), lend support to the existence of within-individual trade-offs in resource allocation. Again supporting such trade-offs, in decorated crickets, *Grylodes sigillatus*, immune challenged males make smaller spermatophores (which are discrete, sperm-containing ejaculate packages), while inducing elevated spermatophore production experimentally reduces immune capacity (Gershman et al., 2010; Kerr, Gershman, & Sakaluk, 2010). The commonality of negative relationships between measures of immunity and ejaculate quality suggests a widespread trade-off between these traits, with compromised immunity being a cost of producing a high quality, competitive ejaculate. Nevertheless, the molecular-genetic mechanisms that underpin these potential trade-offs remain largely opaque.

2.2 Antagonistic pleiotropy between sperm success and immune capacity

Another reason why sperm success and male immune capacity may show a negative association is because of constraints on fitness maximization imposed by genetic architecture. Antagonistic pleiotropy occurs when a single gene affects multiple traits related to fitness, and some allelic variants promote fitness through one trait while compromising fitness through others. Antagonistic pleiotropy could prevent males from simultaneously reaching individual optima for sperm function and immunity if genes have shared immunity and sperm-related functions. An example of this may be Thioester-containing Protein 1 (TEP1), which contributes to immune defense against malaria parasites in the mosquito *Anopheles gambiae* (Blandin et al., 2004). The same protein is also involved in the removal of aberrant sperm in the testes, which is important for ensuring male fertility. Remarkably, the allelic variant that promotes male fertility also renders mosquitoes more susceptible to malaria (Pompon & Levashina, 2015). If such phenomena are widespread, sperm-immunity trade-offs could arise through shared genetic function and antagonistic pleiotropy, as opposed to through resource allocation. This particular example may also provide evidence of genetic antagonism between the sexes, because only female *A. gambiae* are exposed to malaria parasites via blood-feeding, since males do not feed on blood.

2.3 Vertebrate male sperm auto-immunity

Roughly 1000 genes in the mouse genome have been detected as being active primarily in germ cells in the testis (Miyata et al., 2016). The protein products of many of these genes have been detected on the surface of sperm, serving as potential antigens (Tokuhiro et al., 2012). The existence of sperm-specific molecules creates the possibility that, in organisms with acquired immunity (i.e., vertebrates), males could generate antibodies against their own sperm, leading to infertility by targeting their own developing or mature sperm cells. Male vertebrates possess a range of traits to prevent the development of anti-sperm auto-antibodies. These traits include the blood-testis barrier, which prevents the immune system from encountering germ cell-specific antigens that arise during spermatogenesis (Cheng & Mruk, 2012). If this system breaks down, anti-sperm antibodies can be produced, causing immune infertility (Bohring & Krause, 2003). The “sperm protection hypothesis” suggests that immunosuppression by testosterone directly benefits sperm by protecting them from the male’s immune system (Hillgarth, Ramenofsky, & Winfield, 1997). A meta-analysis of human studies lends empirical support to this theory, as immunosuppressive corticosteroid treatments reduce anti-sperm antibodies and improve sperm performance (Skau & Folstad, 2005). More generally, selection may act to balance immunocompetence versus the risk of autoimmunity to sperm and potentially other cells. Such compromises are expected to be particularly acute in vertebrates given their acquired immune systems. Invertebrates lack any highly-specific self/non-self-recognition mechanisms, making it seem unlikely that they would recognize sperm as “foreign.” Nevertheless, invertebrates are subject to the general problem of autoimmunity (Schmid-Hempel, 2005), although it is unclear whether sperm would be a particular autoimmune target.

2.4 Effects of infections in males, including STIs, on sperm success

The previous sections have presented a number of ways in which a male's immune system could negatively impact sperm success. The male immune system can also promote sperm success by fighting against sperm-damaging sexually transmitted infections (STIs). STIs are relevant because—by their nature—the causative pathogens are often present in the reproductive organs and thus in close proximity to sperm. STIs have been most studied in humans, and in other animals of economic importance, but evidence suggests that they are taxonomically widespread (Knell & Webberley, 2004; Lockhart, Thrall, & Antonovics, 1996). Some STIs seem to be particularly harmful to sperm. These sperm-damaging STIs include viruses present in human semen, including papillomavirus and the human immunodeficiency virus (HIV) (Dejucq & Jégou, 2001; Lai et al., 1997; Le Tortorec & Dejucq-Rainsford, 2010). Urogenital infections in men can decrease male fertility through various mechanisms. Infections may disrupt local immune regulation and thus be associated with the development of auto-antibodies to sperm, such as those described in Section 2.3. Infections may also cause an obstruction preventing the normal passage of the ejaculate, or may disrupt the function of male accessory glands and thus reduce the quality or quantity of seminal fluid. Additionally, pathogens may damage sperm directly, or via inflammation induced by the infection (Schuppe et al., 2017; Wald, 2005). Some researchers have hypothesized that STI-induced infertility in either sex is an adaptive strategy of STIs (Apari, de Sousa, & Müller, 2014). This argument is based on the idea that sperm success, resulting in fertilization (and in mammals, pregnancy), often contributes to the inhibition of female sexual activity for a period of time. Given that sexual activity is required for STIs present in females to reach new hosts, preventing fertilization can elevate sexual activity and thus STI transmission opportunities. Alternatively, if STIs reduce female polyandry—perhaps by reducing overall health—then males could potentially gain fitness from infecting their mates, if the reduction in sperm competition outweighed the various costs of the STI (Knell & Webberley, 2004; Wardlow & Agrawal, 2018). Similarly, if infection with an STI elevates short-term female reproductive output, benefitting the male that delivers the infection, then males can theoretically evolve lower resistance to STIs (Johns, Henshaw, Jennions, & Head, 2019). However, considerably more work is required to establish whether STI-mediated effects on fertility or behavior represent adaptive strategies for pathogens or their hosts, or are simply side-effects of other actions that are under selection.

Deleterious effects of infections on sperm success need not be local to the reproductive organs. Systemic infections are likely to reduce the overall condition of a male and thus diminish the pool of resources available for producing high quality sperm. As mentioned in Section 2.1, immune-challenged decorated cricket males make smaller spermatophores (Kerr et al., 2010), consistent with an immune-mediated reduction in condition that, in turn, impacts sperm. Negative effects of immune system activation on sperm function have also been seen in great tits *Parus major* (Losdat et al., 2011) and guppies *Poecilia reticulata* (Devigili et al., 2017), lending further support to the idea. However, a similar test in the house sparrow *Passer domesticus*, while demonstrating a negative impact of infection on testosterone, failed to detect harm to sperm quality (Needham et al., 2017). Thus, whether somatic infections negatively impact sperm is likely specific to the host or parasite species, or dependent on the strength of infection.

3. Sperm success and the female immune system

In the next sections, we describe how interactions between sperm and the female immune system can potentially be harmful to sperm (Sections 3.1 and 3.2) but also can be important in determining which particular sperm are successful (Section 3.3) (Fig. 1).

3.1 Female reproductive tract immunity effects on sperm success

The organs of the female reproductive tract are subject to being colonized by pathogens and can also provide a pathway into the body cavity, where pathogen proliferation can wreak havoc, causing major health and fitness consequences (Soper, 2010). The female therefore has multiple adaptations to impede the invasion and proliferation of pathogens in the reproductive tract, or their ascent within it. Physical impediments in the female tract include (1) production of a cleansing outward flow of fluid (in mammals, at least; Mullins & Saacke, 1989), (2) secretion of a thick (viscoelastic) mucus (also in mammals, at least; Taherali, Varum, & Basit, 2018), (3) construction of narrow labyrinths of passages (seen in Muro et al., 2016; Suarez, Brockman, & Lefebvre, 1997; Yaniz et al., 2014). Chemical impediments include (4) acidification of the vaginal fluid in mammals to a level that kills bacterial pathogens (O’Hanlon, Moench, & Cone, 2013) and may also damage sperm. Interestingly, this acidity is known to be produced by bacteria resident in the vagina, particularly *Lactobacillus* spp. (O’Hanlon et al., 2013). (5) Last, and our primary focus, are immunological impediments to pathogen survival. These can include components of the innate immune system (including inflammatory responses, reactive oxygen species, and antimicrobial peptides) that could potentially damage sperm. In addition, because sperm, like pathogens, contain proteins (i.e., antigens) that are foreign to the female, vertebrate females have the potential to develop antibodies to sperm proteins. Potentially, these various types of impediments, presumably evolved for use against pathogens, could block the survival of sperm or their ability to reach the site of fertilization.

Sperm are more adept at circumventing many of these impediments than are most pathogens. First, due to the shape of the sperm and their mechanism of swimming, hydrodynamic interactions of mammalian sperm with the fluid flow in the female tract enable the sperm to orient and swim “upstream” in the tract, toward the site of fertilization (Miki & Clapham, 2013; Tung et al., 2015a, 2015b). Muscle and organ movements in the tract can also facilitate the movement of sperm toward storage sites (in *Drosophila*; Adams & Wolfner, 2007; Avila & Wolfner, 2009; Mattei et al., 2015; and reviewed in Suarez & Pacey, 2006). The evolution of shapes, energetics, or swimming behaviors that allow individual sperm to move faster also include mechanisms by which sperm can cooperate (reviewed in Pizzari & Foster, 2008; Immler, 2008), and in some cases bundle together and swim faster than single sperm (e.g., hooks on deer mouse *Peromyscus maniculatus* sperm head; Moore, Dvorakova, Jenkins, & Breed, 2002). Second, mammalian sperm with normal motility and morphology readily swim through the mucus that fills the cervix of estrous females, as demonstrated in cattle and humans (Anilkumar et al., 2001; Katz, Slade, & Nakajima, 1997). This ability is based, at least in part, on physical hydrodynamic interactions between sperm and the viscoelasticity of the cervical mucus (Katz et al., 1997). Further along the tract, mucous secretions have been detected in the lumen of the oviduct

(Jansen, 1980; Jansen & Bajpai, 1982; Suarez et al., 1997). Transillumination of mouse oviducts reveals that sperm swim quickly within the lumen, despite the presence of the secretions (Suarez, 1987). Third, again in mammals, there is evidence that some labyrinth-like structures that pose physical impediments to most pathogens actually serve as guides to sperm. For example, the microgrooves that line the cervical canal in cattle can provide privileged pathways through the cervix for sperm. These pathways cannot be accessed by some pathogens that cause STIs, such as trichomoniasis (Tung et al., 2015a). Fourth, while sperm are sensitive to destruction by the acidity of the fluid of the vagina, they are protected by pH buffers in the seminal plasma (Fox, Meldrum, & Watson, 1973; O’Hanlon et al., 2013; Owen & Katz, 2005). Additionally, male-derived seminal proteins can help sperm reach and enter (*Drosophila*) or bind to (bovine) sperm storage sites (Avila & Wolfner, 2009; Gwathmey, Ignatz, & Suarez, 2003; Gwathmey et al., 2006; Neubaum & Wolfner, 1999; Bloch Qazi & Wolfner, 2003). In mammals, either the sperm leave the vagina rapidly by swimming into the more neutral mucus in the cervical canal (e.g., humans, cattle; Sobrero & Macleod, 1962) or the male bypasses the vagina altogether and deposits semen directly into the cervix or uterus (e.g., rodents, pigs; Bedford & Yanagimachi, 1992; Hunter, 1981). Finally, in some taxa, males provide their own physical protection for sperm: either placing them within the female inside a spermatophore sac, or covering the sperm with a “coat” that is removed later, during storage (Friedländer & Gitay, 1972; Wedell, 1993).

In producing immune responses, the female is faced with a balance between protecting herself against pathogen invasion versus potentially compromising fertilization. The responses of the innate immune system, including inflammatory responses, rapidly generate protection against pathogens and serve as a first line of defense. This system is activated by small molecular motifs conserved in pathogens, such as bacterial lipopolysaccharides and peptidoglycans, and depends on receptors present on immune cells, particularly Toll-like receptors in mammals and peptidoglycan recognition proteins in insects (e.g., reviewed in Dziarski & Gupta, 2006; Kurata, 2014; Sheldon, Owens, & Turner, 2017). Such molecular motifs are not present on the surface of sperm, but bacteria are commonly introduced to the female tract by the male during mating (Cottell et al., 2000; Schulze et al., 2018; Sidaway, 2016) and could trigger an innate immune response. In addition to inflammatory responses triggered by incidentally introduced microbes, cells of the *Drosophila* female tract, as well as mucosal epithelial cells and neutrophils of the mammalian female tract, produce anti-microbial peptides that can kill some bacteria and viruses (Amjadi et al., 2014). In *Drosophila* at least, further production of these anti-microbial peptides is induced by mating (Kapelnikov et al., 2008; McGraw, Clark, & Wolfner, 2008), which may serve as a first line of defense for the sperm against microbes that may be present in the female reproductive tract, or introduced during mating. However, recent data have indicated that the vagina, uterus, and oviduct of mammals all contain their own resident, and presumably largely commensal, bacterial biomes. Furthermore, sequencing of 16S rDNA from these microbiomes indicates that the composition of bacterial species in the vagina, uterus, and oviduct differ, despite sharing several species (Chen et al., 2017; Moreno & Franasiak, 2017). The effect of these resident bacteria on immunological activity and fertility is not well understood.

In vertebrates, the female tract can also activate acquired immune responses, which enlist specific antibodies in the defense against pathogens. As in males, females can develop anti-sperm antibodies, but in females the sperm surface proteins in the reproductive tract are non-self and thus clear potential antigens (Tokuhiro et al., 2012). Although sperm-surface antigens could theoretically always provoke an immune response, only 2–3% of women are estimated to produce anti-sperm antibodies (Clark & Schust, 2013). However, in this subset of women anti-sperm antibodies have long been identified as a likely cause of infertility (Dondero et al., 1993; Meaker, 1922). A higher frequency of immunoglobulins IgG and IgA is found on cervicovaginal secretions and sera of women with fertility problems in at least some populations, providing further evidence of their potential role in infertility (Mahdi et al., 2011; Lu, Huang, & Lu, 2008; but see Vujisi et al., 2005). In estrous cervical mucus, anti-sperm antibodies are usually at levels far below those in the bloodstream (Stern et al., 1992). However, mucus samples containing anti-sperm antibodies are known to inhibit movement of sperm (Chiu & Chamley, 2004), suggesting a potential infertility mechanism.

Involvement of acquired immune responses in differential fertilization success is also well established in birds. In domestic fowl, *Gallus domesticus*, female exposure to sperm leads to an immune response, which can reduce the fertilizing efficiency of inseminations. For example, experimental injection of testicular material into hens depresses the fertility of females for the following 12–67 days (McCartney, 1923). This response to sperm exposure is associated with rising levels of sperm antibodies in blood plasma and specifically in serum levels of sperm agglutinins, which modulate sperm agglutination in vitro (Hosoda, Abe, & Otsuka, 1964; Wentworth & Mellen, 1963; see Haley & Abplanalp, 1970 and Burke, Rieser, & Shoffner, 1971 for similar patterns in turkeys, *Meleagris gallopavo*, and Japanese quails, *Coturnix japonica*, respectively). However, it remains unclear whether these same patterns of agglutination occur in vivo, or whether agglutination harms sperm success.

Avian IgY (the equivalent of mammalian IgG) appears to play a particularly important role in female anti-sperm responses in birds. For example, an excess of sperm recovered from the vagina of domestic fowl hens following insemination are bound by IgY compared to sperm recovered from the distal end of the female reproductive tract (the infundibulum), where fertilization occurs, suggesting that IgY may be implicated in targeting sperm (Steele & Wishart, 1992). Interestingly, antibodies bound to sperm are also found in experimentally inseminated hens who had never before mated, suggesting that immunity against other antigens (e.g., pathogens) may have cross-reactivity, causing sperm targeting (Bakst, 2011). Similarly, turkey hens with low fertility expressed IgY on the epithelium of their sperm storage tubules, a site that is typically immunosuppressed (Bakst, 2011; Das, Isobe, & Yoshimura, 2008) and where IgY is not expressed in hens with high fertility (Kirk et al., 1989). In some lines of domestic fowl, female infertility is associated with infiltration of lymphocytes in the sperm storage tubules as well as high numbers of antigen-presenting cells (Ia + cells), and T cells (CD4+, CD8+) (Das, Nagasaka, & Yoshimura, 2005), while in Japanese quails, insemination is followed by a rapid increase of leukocytes (neutrophils and lymphocytes) in the utero-vaginal junction, some of which are in close contact with the inseminated sperm, suggesting that female immune reactions could negatively affect sperm following mating (Higaki et al., 1995).

To avoid the problem of anti-sperm antibodies causing infertility, it seems likely that the innate immune system is especially active as a defensive system in the female tract of mammals, as it is in insects such as *Drosophila*. The male-derived strategy of moving sperm rapidly out of the vagina, or bypassing the vagina altogether in species such as bedbugs, where males inseminate directly into the body cavity (but see Reinhardt, Naylor, & Siva-Jothy, 2003), is also thought to help evade local female immune responses (Suarez, 2015). Combined with the deposition of large numbers of sperm this strategy could also increase the chance that some sperm will survive those attacks. In some insect species, such as *Drosophila pseudoobscura* and some lepidopterans, the male introduces two types of sperm into the female: “eusperm,” which are functional for fertilization, and the more numerous “parasperm,” which are thought to act as decoys against harmful molecules in the reproductive tract and perhaps titrate out such molecules (Holman & Snook, 2006, 2008; Swallow & Wilkinson, 2002). Mammals also appear to use a “strength-in-numbers” strategy: large numbers of inseminated sperm reach the mammalian uterus, and from there thousands or tens of thousands pass into the lower oviduct (Overstreet & Cooper, 1978; Suarez et al., 1997). In response to the large numbers of sperm that enter the uterus, an innate immune response eventually builds up in the uterine cavity. Large numbers of neutrophils enter the cavity to trap and kill sperm by extruding DNA extracellular traps (Alghamdi & Foster, 2005; Zambrano et al., 2016) and phagocytosing sperm (Hong et al., 2017). In this way, the neutrophils eventually clear sperm from the uterine cavity, helping to prepare the uterus for implantation (Troedsson et al., 2001).

3.2 Immunity and sperm storage in females

Although sperm-use often begins relatively rapidly after copulation, in many species sperm can be stored for some period before use—typically days or weeks—but in some species up to years (reviewed in Orr & Brennan, 2015; Orr & Zuk, 2012; Schnakenberg, Siegal, & Bloch Qazi, 2012). In particular, females of invertebrate taxa, such as insects, commonly store sperm in specialized organs, such as seminal receptacles and spermathecae, that bud off the main conduit in the female tract, and may provide protected sites for the sperm. However, many female mammals also contain sperm reservoirs, where sperm can be maintained alive prior to ovulation, for up to a few days in most species (up to 5 days in humans; Holt & Fazeli, 2016), or as long as throughout the winter during hibernation in the some bats (Racey et al., 1987; Suarez & Pacey, 2006). In storage reservoirs, sperm speed and numbers would not likely be sufficient to protect sperm against immune responses. Given that the female immune system has the potential to destroy sperm, storage organs must therefore protect sperm from the female’s own immunity, presumably by being areas of low immunological activity (reviewed in Orr & Brennan, 2015). Although mammalian sperm are held in the storage reservoir of many (if not all) species by binding to the mucosal epithelium, and thus are exposed to fluid contents of the female tract, here they seem protected against attack by the innate immune system. In cattle, binding of sperm to oviductal mucosal epithelium in vitro upregulates expression of anti-inflammatory cytokines (*TGFB1* and *IL10*) in the epithelial cells (Yousef et al., 2016) which may help to protect sperm from harmful immune action. Still, much remains to be learned about how the immune system may be repressed in the oviduct during sperm storage and how epithelium binding helps maintain vitality of the sperm (Suarez, 2016).

Several studies on insects provide evidence of interplay between female immunity and sperm in storage. Experiments using the field cricket *T. oceanicus* provide evidence that experimental bacterial infections in females reduce the viability of sperm in storage (McNamara, van Lieshout, & Simmons, 2014), while in *D. melanogaster*, stimulation of the immune system using a pathogen mimic (peptidoglycan) results in reduced viability of stored sperm (Radhakrishnan & Fedorka, 2012). Effects of infections on stored sperm viability could arise through one of several mechanisms. First, the impact of infection on stored sperm could represent a resource trade-off in female investment between immune responses versus investment in maintaining the viability of sperm in storage. However, in *D. melanogaster*, sperm survive well in spermathecae dissected out of the female body. Given that removed organs are cut-off from somatic resources this finding argues against a trade-off (Radhakrishnan & Fedorka, 2012). Second, it may be that the bacteria interact with—and harm—the sperm directly. In vitro studies using bed bug *Cimex lectularius* sperm show that incubation with environmental microbes damages sperm (Otti, McTighe, & Reinhardt, 2013), raising the potential they may also be able to do so in vivo. Finally, sperm may be harmed as a side-effect of the female's immune response, for example, if the by-products are especially toxic to sperm (McNamara et al., 2014; Radhakrishnan & Fedorka, 2012). Males may thus act to suppress the female immune system. Evidence in the cricket, *Allonemobius socius*, is consistent with the idea that the male ejaculate interferes with the female immune system, potentially to help prevent sperm from being harmed (Fedorka & Zuk, 2005). Studies of *D. melanogaster* have also revealed an increase in the frequency of empty sperm storage organs in females that had mated to males whose genitalia had been dipped in peptidoglycan, which thus might approximate a male infected with an STI (Radhakrishnan & Fedorka, 2012). These data suggest that females eject the sperm of these “infected” males from their storage organs, perhaps to remove dead sperm or avoid further infection, raising the possibility that STI-infected males suffer an additional loss of sperm success via female rejection of their sperm from storage.

Comparable patterns have been seen in other insect species. A negative relationship between sperm storage and immunity occurs in a species with extreme long-term sperm storage: the ant, *Atta colombica*. *Atta queens* can live for decades, and it is thought that their reproductive success is at least partly limited by the ability to store sufficient numbers of sperm, which are required to fertilize eggs to produce workers for the colony. In this species, females found with more sperm in storage, and who store the sperm of more males, display a lower encapsulation response (the surrounding of pathogens and parasites with layers of dead melanized hemocytes), which is consistent with costs arising from storing sperm in general, and from encountering multiple male genotypes (Baer, Armitage, & Boomsma, 2006). However, being a correlational result, it is also possible that females who display lower encapsulation responses tend to mate with more males and store more sperm. Either way, the work highlights that sperm storage and immunity are often intimately—and negatively—associated.

3.3 The role of female immunity in post-copulatory sexual selection: Immune-mediated cryptic female choice

The high potential for female immune responses to sperm, as outlined above, presents the opportunity to generate post-copulatory sexual selection. As described earlier, where females mate with more than one male (which is very common; reviewed in Taylor, Price, & Wedell, 2014), the sperm of different males can compete for fertilization opportunities in sperm competition (Parker & Pizzari, 2010; Wigby & Chapman, 2004). However, this situation also creates the conditions necessary for cryptic female choice (CFC) whereby females generate a systematic bias in the paternity share of competing males (Eberhard, 1996; Firman et al., 2017), and there are good reasons to believe that CFC can occur via the female immune response. Here, we briefly discuss: (1) the scope for immune-mediated CFC across taxa, (2) the adaptive significance and functional causes of immune-mediated CFC, (3) underpinning immunological mechanisms, and (4) evolutionary consequences.

The scope for female immunity to drive CFC is strongly dependent on taxon and reproductive system. In external fertilizers, where partner interactions are limited or altogether absent, female immunity is expected to have a limited role in post-copulatory sexual selection, although immune factors on the egg could potentially influence fertilization patterns via differential sperm chemotaxis (Eisenbach & Giojalas, 2006; Evans et al., 2012). Female immunity is expected to be more important in internal fertilizers, particularly those with prolonged female sperm storage and acquired immune responses where responses have the potential to be dynamic and change over time.

Three non-mutually exclusive scenarios could drive immune-mediated CFC. Immune-mediated CFC may represent an adaptive female strategy for (1) her own viability, by neutralizing ejaculates that contain pathogens, or in response to ejaculate traits with harmful effects on females (Morrow & Innocenti, 2012) or (2) increasing the fitness of her offspring, by selecting sires that maximize offspring viability or reproductive success. Alternatively (3) immune-mediated CFC could be a non-adaptive by-product of some other naturally-selected function, e.g., resistance against certain pathogens/parasites may generate an immune predisposition against the sperm of certain male phenotypes. A bias in paternity share is selected for only in the second hypothesis, while it is a non-adaptive consequence in the other two.

One class of genes that has been hypothesized to play a particularly important role in immune-mediated CFC is the Major Histocompatibility Complex (MHC), also known as Human Leukocyte Antigen (HLA) complex in humans. The MHC plays a fundamental role in vertebrate acquired immunity by enabling antigen presentation to T cells and self versus non-self recognition. The extreme polymorphism of the MHC has long attracted evolutionary explanations, including a role for sexual selection (Edwards & Hedrick, 1998). In principle, females may be able to optimize the MHC of their offspring by biasing fertilization in favor of sperm or ejaculates with certain MHC haplotypes (Firman et al., 2017; Milinski, 2006; Ziegler, Kentenich, & Uchanska-Ziegler, 2005). Consistent with this idea, Zheng et al. (2001) found that insemination upregulated MHC class II genes, in certain regions of the female reproductive tract of domestic fowl hens. MHC class II genes code for molecules involved in the recognition and presentation of extracellular antigens by antigen-

presenting cells, and thus represent the class of MHC that one would expect to be involved in recognition of sperm antigens. Løvlie et al. (2013) found that female red junglefowl, *Gallus gallus*, retain more sperm following natural mating by males that are less MHC-similar, suggesting that female fowl select against the sperm of genetically related males to avoid inbreeding, as indicated by previous work (Pizzari, Løvlie, & Cornwallis, 2004). However, further research has failed to find strong evidence that MHC similarity plays an important role in female sperm selection above and beyond inbreeding avoidance (e.g., Collet, 2010). The idea of MHC-based sperm selection finds further empirical support in the externally-fertilizing three-spined stickleback, *Gasterosteus aculeatus*, where fertilization is biased in favor of combinations of gametic MHC haplotypes that maximize offspring viability (Lenz et al., 2018). However, in whitefish, *Coregonus* sp., there is no evidence for MHC effects (Wedekind et al., 2004). One possible explanation of the discrepancy between the Lenz et al. (2018) and Wedekind et al. (2004) studies is that the latter considered MHC genotypes of male and female partners, in contrast to variation in MHC haplotypes of individual gametes, which was used in the former study. An effect of individual MHC sperm haplotypes consistent with the results of Lenz et al. (2018) would require MHC haploid expression in mature sperm cells, although evidence for this remains limited. Thus, the importance of MHC in immune-mediated CFC requires considerably more investigation.

Regardless of underpinning mechanisms, patterns of sperm selection via female immunity may have far-reaching evolutionary implications. Males are expected to evolve strategies to escape female immune responses. For example, it is possible that the abundance of seminal fluid proteins with antimicrobial properties detected in the male seminal fluid of different species (Borziak et al., 2016; Dorus, Skerget, & Karr, 2012) may be partly explained by males attempting to lower the microbial load of an ejaculate in order to reduce the risk of triggering female immune reactions. Other strategies may include masking the antigenicity of the sperm surface through components of the glycocalyx, the matrix of hundreds of glycoproteins and glycolipids that encapsulates the entire sperm cell and plays a key role in sperm transport within the female reproductive tract. The sperm glycocalyx is rich in sialic acids, which tend to occupy the outermost part of the sperm surface. In mammals, highly sialylated glycoproteins such as beta defensins can play a key role for protecting sperm against female antibody binding (Yudin et al., 2005) and phagocytosis by macrophages (Ma et al., 2016). Similarly, in domestic fowl, experimental desialylation leaves sperm functionally intact in vitro but prevents them from moving through the female vagina following insemination (Steele & Wishart, 1992). These patterns indicate that sialic decoration of the sperm glycocalyx may have evolved at least partly as a male adaptation to evade anti-sperm female immune responses (Ma et al., 2016).

These tight coevolutionary immune interactions between sperm and female reproductive tract may in turn contribute post-copulatory prezygotic reproductive isolation and ultimately speciation. For example, Ghaderi et al. (2011) recently presented compelling evidence of prezygotic reproductive barriers mediated by female immune responses against the sperm glycocalyx in mammals. Humans lost the ability to produce a type of sialic acid common in other mammals, the *N*-glycolylneuraminic acid (Neu5Gc), approximately 3 million years ago, and are now capable of producing Neu5Gc-specific antibodies. Female mice immunized to express anti-Neu5Gc antibodies suffer from lower fertility when mated with

transgenic Neu5Gc-positive males. Moreover, human anti-Neu5Gc antibodies target Neu5Gc antigens on the sperm of chimpanzees, *Pan troglodytes*, and kill these sperm. Thus, female immunity against Neu5Gc-carrying sperm may have played an important role in human evolution by creating reproductive isolation in ancestral polymorphic hominin populations (Ghaderi et al., 2011). Female immune responses to sperm have also been advocated to explain patterns of post-copulatory pre-zygotic reproductive isolation in bird populations, such as between Japanese quails and domestic fowl, mediated by female differential sperm agglutination (Haley & Abplanalp, 1970), and between collared flycatchers, *Ficedula albicollis*, and pied flycatchers, *F. hypoleuca*, mediated by acquired immunity (Cramer et al., 2016).

Collectively, these empirical results indicate that female anti-sperm antibody responses have the potential to systematically bias the outcome of sperm competition, with potentially far-reaching ramifications for inter-sexual coevolution and speciation. These responses, however, are likely to be complex and temporally dynamic, and to date, the extent of immune-mediated CFC remains to be defined.

4. Conclusions

It is clear that sperm success and immunity are linked in varied ways, from the onset of spermatogenesis in the male, through to the moment of fertilization in the female (in internal fertilizers). However, our review has identified many gaps that remain in our current knowledge. For example, although several lines of evidence suggest that males often face resource trade-offs between investing in immunity versus investing in sperm production the mechanisms underpinning resource trade-offs remain opaque. One potentially fruitful future approach may be to use isotope labeling of molecular components of food, for example, heavy lysine (de Godoy, 2014), and track where those molecules end up. By quantifying the amount of consumed material in testes versus immunoactivity organs, it may be possible to test the idea that resource use by sperm and the immune system is a zero-sum game. A similar approach may help us better understand the costs of sperm storage in females.

Although testosterone has long been invoked as a potential hormonal mediator of the immunity versus sperm trade-off in vertebrates, our understanding in invertebrates lags behind. Juvenile hormone is a broad scale mediator of immunity and reproduction in insects (Schwenke, Lazzaro, & Wolfner, 2016), yet its relevance for direct impacts on sperm remains little studied, and ripe for investigation. Similarly, whereas anti-sperm immunity in both females and males clearly plays a key role in fertility in vertebrates, we know very little about whether immune systems directly impact sperm in invertebrates. Again, this is an area ripe for investigation, with studies at cellular level likely to provide us the biggest advances in knowledge.

Antagonistic pleiotropy, or more broad negative epistatic effects between genes involved in immunity and sperm, remains almost entirely the subject of speculation, with very little data to go on. As our general functional genetic understanding of model organisms improves, we may stumble upon examples, but the field lacks the same investment as has been seen in aging, where 100s of candidates of antagonistic pleiotropy between senescence and early

life-benefits have been identified (Austad & Hoffman, 2018). Even a much more modest effort to understand the shared genetics of immunity and male sperm success would provide a considerable new insight into the mechanisms linking immunity and sperm, with potentially large benefits to the fields of disease and reproductive biology.

STIs clearly impact fertility in many cases, often via harmful effects on sperm. A key current question is whether STIs harm sperm as an adaptive strategy, to promote their own transmission, or merely as a side effects of other aspects of their biology. Answering this question will likely require development of mathematical theory (e.g., Johns et al., 2019) as well as careful empirical experimentation, particularly in short-lived lab systems that allow observation of experimental evolution.

It is certain that the immune systems of both the female and male present a risk to sperm, particularly in species with acquired immunity. It is perhaps remarkable that males and females avoid complete destruction of the sperm and remain fertile. Although we have some understanding of how females and males protect sperm from their own immune system, much remains to be discovered about sperm protection and about what makes the mechanisms break down, leading to infertility. The intriguing possibility that immune targeting of sperm could be co-opted by females to discriminate among the sperm of different males has far-reaching ramifications for evolution. Progress in identifying the discrimination among specific sperm phenotypes and genotypes by the female immune system may require novel approaches such as labeling the sperm of individual males, or haploid subsets of sperm, in order to directly visualize their fate within the female immune environment.

Acknowledgments

We thank Ruth Lehmann for the invitation that allowed us to probe this interesting topic together. The literature in this field is large, and we apologize to those authors whose excellent work could not be cited here due to space limitations. We thank the following sources for support: NIH grants R01-HD038921 (M.F.W.) and R01-HD059060 (M.F.W. and AG Clark), a BBSRC fellowship to S.W. (BB/K014544/1), and an industrial LINK award from the BBSRC and Aviagen® to T.P. (BB/L009587/1).

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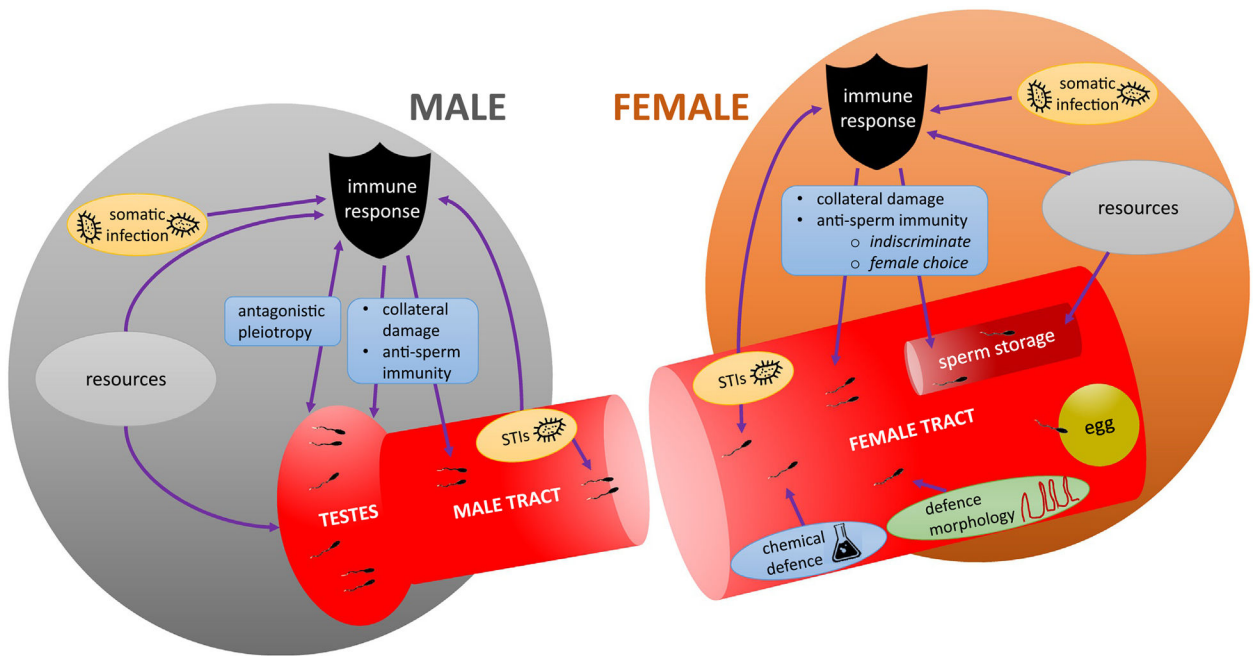


Fig. 1.

Schematic of the interplay between immunity and sperm success in males and females. Resources may trade-off between the immune system and the production of sperm in males, and the protection of sperm in storage in females, leading to sub-maximal trait values. Trade-offs could also come about genetically: genes of shared male immune and sperm-related function could generate antagonistic pleiotropy, preventing simultaneous maximization of both traits. STIs can harm sperm directly, and thus immune defense against STIs could protect sperm. However, immune responses to STIs or somatic infections could also harm sperm as a side-effect of their defensive actions, causing collateral damage to sperm. Immune responses may negatively impact sperm directly, particularly in vertebrates via anti-sperm antibodies, both in females, and in males as an auto-immune response. Female immune responses may indiscriminately harm sperm, which could contribute to infertility, or they may form part of adaptive female choice, selecting out the sperm of disfavored males after mating, but before fertilization. Within the female reproductive tract sperm interact with the chemical and morphological environment—which is likely be designed to inhibit pathogen proliferation, and may help or hinder the sperm—on the way to sperm storage sites and fertilization.